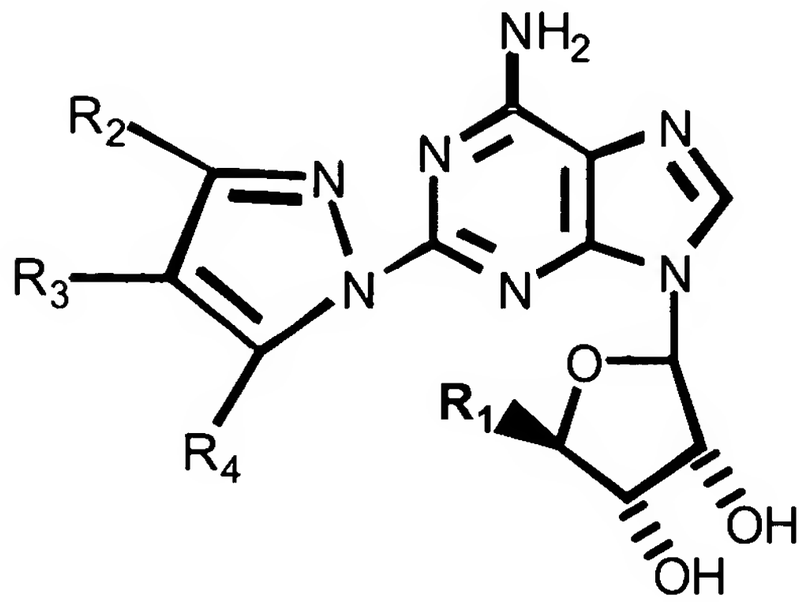
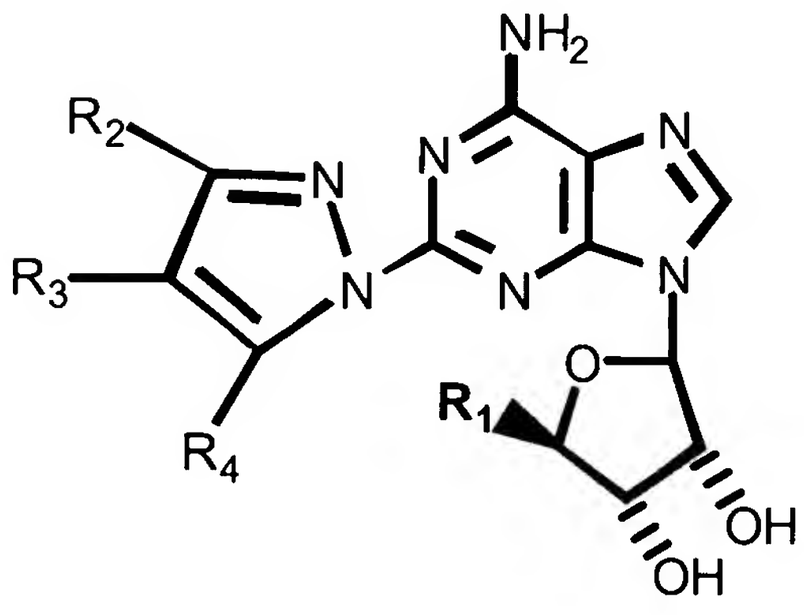
APPENDIX B

Clean Claims Pending After Response to Office Action




1.(Once Amended) A compound having the formula:




wherein $R^1 = CH_2OH$;

$R^3$ is selected from the group consisting of $CO_2R^{20}$, $-CONR^7R^8$, and aryl, wherein the aryl substituent is optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, alkyl, and $OR^{20}$;

$R^7$ is selected from the group consisting of hydrogen, straight or branched $C_{1-15}$ alkyl and $C_{3-8}$ cycloalkyl, wherein the alkyl substituent is optionally substituted with from 1 to 3 substituents independently selected from the group consisting of aryl and $CO_2R^{20}$, and wherein the optional aryl substituent is optionally substituted with halo;

$R^8$ is selected from the group consisting of hydrogen, straight or branched $C_{1-15}$ alkyl and $C_{3-8}$ cycloalkyl ;

$R^{20}$ is selected from the group consisting of hydrogen and $C_{1-15}$ alkyl; and

wherein $R^2$ and $R^4$ are hydrogen.

2. (Once Amended) The compound of claim 1 wherein $R^3$ is $CO_2R^{20}$; and $R^{20}$ is selected from the group consisting of hydrogen and $C_{1-4}$ alkyl.

3. (Once Amended) The compound of claim 1 wherein $R^3$ is $CONR^7R^8$ ;

$R^7$ is selected from the group consisting of hydrogen, straight or branched $C_{1-10}$ alkyl and $C_{3-5}$ cycloalkyl, wherein the alkyl substituent is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of aryl and $CO_2OR^{20}$;

$R^8$ is selected from the group consisting of hydrogen, straight and branched $C_{1-3}$ alkyl and $C_{3-5}$ cycloalkyl; and

$R^{20}$ is selected from the group consisting of $C_{1-4}$ alkyl.

4. (Once Amended) The compound of claim 1 wherein $R^3$ is aryl, wherein the aryl substituent is optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, alkyl and $OR^{20}$; and

$R^{20}$ is selected from and the group consisting of $C_{1-4}$ alkyl.

5. (Once Amended) The compound of claim 2 wherein $R^3$ is $CO_2R^{20}$; and

$R^{20}$ is selected from the group consisting of hydrogen and $C_{1-4}$ alkyl.

6. (Once Amended) The compound of claim 3 wherein $R^7$ is selected from the group consisting of hydrogen, $C_{1-3}$ alkyl and cyclopentyl, wherein the alkyl substituent is optionally substituted with from 1 to 2 substituents, independently selected from the group consisting of phenyl and $CO_2R^{20}$and wherein each optional phenyl substituent is optionally substituted with halo;

$R^8$ is selected from hydrogen and methyl; and

$R^{20}$ is selected from hydrogen and ethyl.

7. (Once Amended) The compound of claim 4 wherein

$R^3$ is aryl, wherein the aryl substituent is phenyl optionally substituted with from 1 to 2 substituents independently selected from the group consisting of chloro, methyl and $OR^{20}$;and

$R^{20}$ is methyl.

19. (Once Amended) The compound of claim 1 selected from the group consisting of ethyl 1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazole-4-carboxylate;

(4S,2R,3R,5R)-2-{6-amino-2-[4-(4-chlorophenyl)-pyrazolyl]purin-9-yl}-5-(hydroxymethyl)oxolane-3,4-diol;

(4S,2R,3R,5R)-2-{6-amino-2-[4-(4-methoxyphenyl)pyrazolyl]purin-9-yl}-5-(hydroxymethyl)oxolane-3,4-diol;

(4S,2R,3R,5R)-2-{6-amino-2-[4-(4-methylphenyl)pyrazolyl]purin-9-yl}-5-(hydroxymethyl)-oxolane-3,4-diol;

(1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)-N-methylcarboxamide;

1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazole-4-carboxylic acid;

(1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)-N,N-dimethylcarboxamide;

(1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)-N-ethylcarboxamide;

1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazole-4-carboxamide;

1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)-N-(cyclopentyl)carboxamide;

(1-{9-[(4S,2R, 3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)-N-[(4-chlorophenyl)methyl]carboxamide; and

Ethyl 2-[(1-{9-[(4S,2R, 3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-

aminopurin-2-yl}pyrazol-4-yl)carbonylamino]acetate.

20. (Once Amended) A method for stimulating coronary vasodilation in a mammal by administering by intravenous bolus injection an amount of a compound of claim 1 that is sufficient to stress the heart and induce a coronary steal situation for the purposes of imaging the heart.

22. The method of claim 20 wherein the mammal is a human.

23. (Once Amended) A pharmaceutical composition comprising a compound of claim 1 and one or more pharmaceutical excipients.

24. The pharmaceutical composition of claim 23 wherein the pharmaceutical composition is in the form of a solution.

25. (Once Amended) The pharmaceutical composition of claim 23 for the treatment of inflammation, in adjunctive therapy with angioplasty, platelet aggregation, and platelet and neutrophil activation.

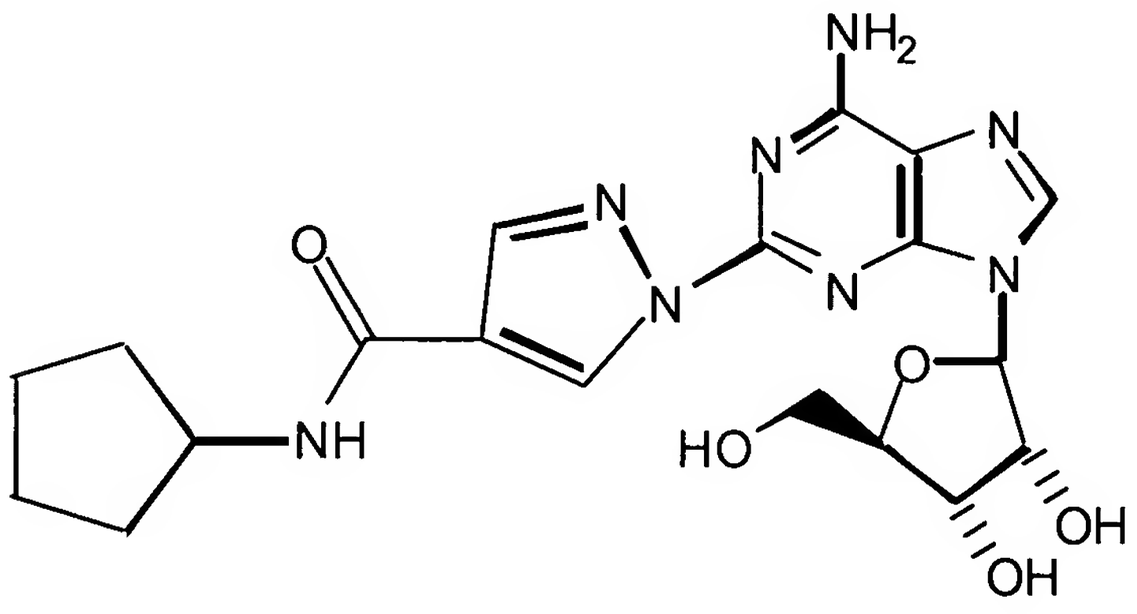
26. (New) The compound of claim 19 wherein the compound is (1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)-N-methylcarboxamide.

27. (New) The compound of claim 19 wherein the compound is 1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)-N-(cyclopentyl)carboxamide.

28. (New) The compound of claim 19 wherein the compound is (1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)-N-ethylcarboxamide.

29. (New) A method of dilating the coronary vessels of a mammal, as an adjunct to angioplasty, with the pharmaceutical composition of claim 23.

**Example 10**




**(1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)-N-(cyclopentyl)carboxamide (21)**

Compound **12** (0.5 g, 1.2 mmol) was dissolved in dry DMF, TBDMSCl (1.5 g, 10 mmol) and imidazole (0.68 g, 10 mmol) were added and the mixture was heated at 80 $^0$C for 24 h. The solvent was evaporated and the residue was purified by flash column to obtain the trisilyl protected form of compound **12**. The trisilyl derivative (0.8 g) was then suspended in 1 mL of water and treated with 2 mL1N KOH/MeOH. The mixture was stirred at RT for 72. The solvent was removed under reduced pressure and the residue was suspended in 5 mL of water and acidified to pH 5.5 with 1N HCl. The resulting precipitate was filtered and washed with water and ethyl ether to afford the trisilyl form of the acid **20**.

The trisilyl derivative acid **20** ( 0.14 g, 0.2 mmol) was then dissolved in 5 mL dichloromethane. To the solution was added HBTU (0.19 g, 0.4 mmol), HOBt (.076 g, 4 mmol), N-methylmorpholine (0.04 g, 0.4 mmol) and cat. DMAP. The mixture was allowed to stir at RT for 24 h. The mixture was then washed with 10% citric acid, saturated $NaHCO_3$, brine and dried over $MgSO_4$. The solvent was removed and the residue was treated with 5 mL 0.5N $NH_4F$/MeOH. The solution was heated at reflux for 24 h. The solvent was evaporated and the residue was purified by preparative TLC to afford compound **21,** MS 445.26 (M+1).

| | | | |
|---|---|---|---|
| WRC-470 (1μ/kg/min) | 9.5±0.8 | 22.5±1.6 | 6 |
| GSC21680 (2μg/kg/min) | 9.7±0.8 | 21.4±0.8 | 3 |
| YT-146 (1μ/kg/min) | 17.8±3.4 | 32.9±5.6 | 3 |

Time (in minutes) to 50% and 90% (t 0.5 and t 0.9' respectively) reversal of the increases in coronary blood flow caused by adenosine receptor agonists. Values are the means:!: SEM of one or two determinations in each animal (n).

Compound 16 is a low affinity $A_{2A}$AdoR agonists and less potent ( -10-fold) than the prototypical agonist CGS21680. Nevertheless Compound 16 is a full agonist to cause coronary vasodilation. But, as shown in this study the duration of its effect is several-fold shorter than that of the high affinity agonists CGS21680 and WRC-0470. Hence, Compound 16 is a short acting $A_{2A}$ AdoR agonists coronary vasodilator. Because of its short duration of action in comparison to the high affinity $A_{2A}$AdoR agonists (e.g., WRC-0470, CGS21680) this low affinity but still full agonist coronary vasodilator may prove to be ideal pharmacological "stressor agents" during radionuclide imaging of the myocardium.

## Experimental Reagents

Table 8 lists the $A_{2A}$ adenosine agonists and antagonists that were used in Examples 14-18.

**Table 8. Biologically Active $A_{2A}$denosine Receptor Agonists and Antagonists.**

| Compound | Abbreviation | Activity |
|---|---|---|
| 5'-N-ethylcarboxamidoadenosine | NECA | $A_{2A}$ agonist |
| N-[(1R)-1-methyl-1\2-phenylethyl]adenosine | R-PIA | $A_{2A}$ agonist |
| 8-cyclopentyl-1,3-dimethylxanthinge | CPX | $A_{2b}$ antagonist |
| 4-[2-[[6-Amino-9-(ethyl-B-D ribofuranuron-amindosyl)-9H-purin-2-yl]aminoethyl]benz-enepropanoic acid | CGS21680 | $A_{2A}$ adenosine receptor agonist |
| N-ethyl-1'-deoxy-1'-(6-amino-2-hexynyl-9H-purin9-yl)-beta-D-ribofura nuronamide | HENECA | $A_{2a}$ adenosine receptor agonist |
| 2-alkynyladenosine | YT-0146 | $A_{2a}$ adenosine receptor agonist |
| 2-cyclohexylmethylidenehydrazinoadenosine | WRC0470 | receptor agonist |
| 4-(2-[7-amino-2-(2-furyl)[1,2,4]triazolo[2,3-a][1,3,5]triazin-5-ylamino]ethyl)phenol | ZM241385 | $A_{2A}$ adenosine receptor antagonist |